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Chromium and Disease: Review of Epidemiologic Studies with Particular Reference to Etiologic Information Provided by Measures of Exposure

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Dozens of epidemiologic studies have been conducted since the late 1940s in an attempt to elucidate the relationship between exposure to chromium compounds and increased rates of certain cancers observed in several industries. The relationship between employment in industries producing chromium compounds from chromite ore and lung cancer has been well established in numerous studies. The relationship between exposure to certain chromium-based pigments and chromic acid and lung cancer, although not as strong, is fairly well accepted. The data concerning emissions from stainless-steel manufacturing and disease are contradictory. Although individual studies have indicated excesses of gastrointestinal and occasionally other cancers in these industries, results are not consistent and not universally accepted. There is general agreement that chromite ore does not have an associated risk of cancer. Although the chromium compound (or compounds) responsible for disease have yet to be identified, there is general agreement that hexavalent species are responsible for these diseases and that the trivalent species are not. Hypotheses about the carcinogenicity of specific chromium compounds generally relate to their solubility in body fluids. These hypotheses, however, have generally been produced as a result of toxicologic, not epidemiologic, investigation. Well-designed epidemiologic studies incorporating detailed assessments of worker exposures have the potential to help elucidate causality, identify specific carcinogenic compounds, and quantify risk in humans, eliminating the need to extrapolate from animal data. Although the need for exposure data crucial to this effort was identified in the earliest epidemiologic studies of chromium, such studies have not been conducted. As a result, little more is known today about the relationship between this chemical and disease in humans than was known 40 years ago.

Introduction

Chromium and chromium compounds have been the subject of more epidemiologic investigations than any other chemical, with the possible exceptions of asbestos and benzene. Chromium chemicals were among the earliest chemicals recognized to be carcinogenic in humans. Indeed, the health consequence of occupational exposure to chromium was the subject of the earliest modern-day epidemiologic studies. Epidemiologic investigation of chromium and its compounds continues to this day. During this long period of study, the relationship between exposure to chromium species and lung cancer has been well established in some industries. The relationship is more tenuous for other industries, other species, and other disease sites. Despite this long period of epidemiologic investigation, exactly which compounds are carcinogenic has not been resolved. Little progress has been made toward resolving this problem in the last 40 years, in large part because few epidemiologic studies have included satisfactory measures of exposure to help unravel the disease puzzle.

In recent years several excellent reviews of epidemiologic studies of workers exposed to various chromium chemicals have been published *(1,2)*. It is the purpose of this paper to reexamine the relevant epidemiologic studies to evaluate etiologic information that may be gleaned from the exposure information presented. Because of the general paucity of relevant quantitative exposure information, epidemiologic investigators must typically rely on some surrogate of exposure, which makes understanding causation and quantitative risk assessment impossible. Despite numerous statements that exposure data must be evaluated as a

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part of epidemiologic studies, this practice is rare. Braver et al. (3) represent the only published attempt in the chromium literature to quantify risk through the use of exposure data collected in one chromate-producing plant by the local health department. Unfortunately, because these data were collected for compliance purposes (i.e., with the purpose of documenting overexposures as compared to some guideline or regulation), their adequacy for epidemiologic purposes cannot be determined. In addition, these data do not provide any information as to species-specific risks.

Background

Classic case-control and proportionate mortality epidemiologic investigation of the relationship between exposure to a chemical and resultant disease uses simple classification of subjects as exposed or nonexposed. Clearly, there is a wide range of exposures, measured both in intensity and duration, encompassed under this rubric. This heterogeneity of exposures, and the possible misclassification of nonexposed persons, will dilute measures of the strength of any relationship that exists. In addition, the results of these studies may not be used to quantify the risk of disease and are very insensitive tools for the identification of the causative agent.

Carefully constructed cohort studies, on the other hand, when provided with detailed relevant exposure information on the study population, can be used for quantitative risk assessment and to identify causative agents. Unfortunately, sufficient, if any, relevant exposure data are rare. This is especially true for studies of cancer in which the relevant exposures occurred decades before the study was undertaken. In the absence of exposure data, epidemiologists are forced to rely on surrogate measures of exposure. Surrogates such as duration of employment or subjective classification of jobs as having high, medium, or low exposure are often used. These measures have been used successfully to identify exposure-response relationships in the population, an indication that the association observed is real. The ability of this type of study to accurately quantify risk is limited due to the heterogeneity of worker exposures in time and space and the ability of the investigator to assign an appropriate exposure value.

The lack of worker exposure information is generally the limiting factor in the quantification of risk from epidemiologic study. Even when historic data are available, they are often of limited use because of poor documentation of the sampling and analytical methods employed, limited information on the conditions during sampling, and the fact that exposure samples have generally been collected for purposes other than epidemiology. The reason for sampling dictates the sampling strategy used. Historically, most air sampling in industrial facilities was conducted in an effort to solve a problem. As such, much historic air sampling may overestimate average exposures (required for epidemiologic risk estimation) considerably.

The need for information on exposures in various chromium industries has long been recognized. The data useful for epidemiologic study, however, remain rare. This paper is a review of the epidemiologic literature on chromium with particular reference to exposure information presented and clues it provides for identifying and quantifying risks. The literature is arranged chronologically by four important industrial sources of exposure.

Chromate-Producing Industries

Chromate production represents the earliest and best-documented relationship between exposure to chromium compounds and lung cancer. Exposures in this industry, which converts raw chromite ore into usable compounds, are to a wide variety of trivalent and hexavalent chromium compounds. The fact that there is not a "pure" exposure in this industry has greatly complicated resolution of the etiologic questions. The basic production process involves the milling and mixing of trivalent chromite ore with lime and soda ash. (Some facilities use a lime-free process.) This mixture is then heated to a high temperature ("roasted"), which oxidizes much of the trivalent chrome to the hexavalent chrome species. The soluble hexavalent species are then extracted with water ("leaching"). This part of the process is known as the dry end. Additional production activities are based on reaction of the sodium chromate leachate produced. All of these processes, usually down to the final crystallization and packing steps, take place in the liquid form; hence, this is known as the wet end. Wet-end production steps vary depending on the desired final product. Typically, a significant proportion of the leachate was converted to sodium bichromate through reaction with sulfuric acid or sodium bisulfate by-product. The sodium bichromate was either sold or used as an intermediate in the production of a variety of chromate chemicals, typically potassium bichromate, chromic acid, and leather tanning agents.

Although case reports describing the association between chromate exposure and lung cancer date from the late nineteenth century, the first systematic epidemiologic assessment of the chromate industry was not conducted until after World War II (4). This study of workers employed in seven chromate-producing plants in the U.S. evaluated risk through analysis of group health insurance records over a period of 10 to 15 years (depending on the plant) prior to initiation of the study. Long-term workers were included. Lung cancer rates were found to be 18 to 50 times normal. Gastrointestinal cancers were elevated over the control group, but to a much lesser degree in two of the plants.

Many of the still unresolved problems of estimating worker chromate exposure for epidemiologic purposes were identified in this early paper (4). It was recognized that exposures relevant to disease production had occurred in the past and that current measures were inappropriate estimators of this exposure. In addition,

the frequent undocumented movement of workers made construction of worker-specific exposure histories impossible. As a result, the investigators were forced to rely on qualitative surrogate measures of exposure, including worker descriptions of past conditions and analysis of time-to-nasal perforation data (thought to be related to air concentrations of hexavalent chromium), to establish that historic exposures were actually higher than current exposures.

Industrial hygiene exposure data were not available for any of these plants prior to 1941. Airborne chromium concentrations were shown to vary widely by department within a plant, and even more widely between plants. For instance, chromium concentrations in the vicinity of the concentrators at the four plants are reported to be 0.02 to 0.20, 0.02, 2.17, and 0.28 to 1.3 mg/m^3, respectively. Little documentation is presented to support the sampling data, although it is noted that samples were collected for control purposes. This might indicate a bias toward higher estimates of exposure. Because of the limited usefulness of the quantitative data, the investigators were forced to rely on duration of employment as a surrogate measure of exposure; a clear dose-response relationship was demonstrated using these data. Differences in manufacturing processes between the plants assumed to relate to exposures were exploited to help explain differences in disease patterns. Based on these differences, in which lung cancer was not observed in a plant that included only liquid bichromate, chromic acid, and tanning agent production, it was concluded that the monochromates were the responsible agent.

Baetjer (*5*) analyzed the lung cancer cases identified by Machle and Gregorius (*4*), numerous German case reports (*5*), and additional cases identified at one of the plants studied by Machle and Gregorius (*4*). Average exposures at new chromate plants were quoted from the German literature to range from 0.1 to 0.5 mg/m^3 chrome, but with variations ranging from 0.1 to 37.2 mg/m^3. Exposures at old plants were quoted to have ranged from 5 to 40 mg/m^3 monochromates and up to 50 mg/m^3 bichromates in old plants. (Exactly how concentrations are expressed in terms of chromium equivalents is unclear from this report; the above data are reproduced verbatim.) The German literature reviewed in this paper (*5*) lists many chromate chemicals suspected to be the causative agent; there is agreement in this literature, however, that because of its insolubility the chromite ore is not the causative agent.

Because of limitations inherent in the Machle and Gregorius study (*4*), Baetjer (*6*) used a case-control design to measure the increased risk of lung cancer resulting from working in a chromate plant. The nature of this design, however, does not permit detailed evaluation of exposure; only exposure status (exposed or nonexposed) is used. This study compared the exposures of 859 cases of lung cancer (290 pathologically confirmed) admitted to two Baltimore hospitals between 1925 and 1946 with two groups of controls. Eleven of the lung cancer cases reported previous exposure to chromium chemicals; ten of these cases had been employed in a local chromate production facility. None of the controls reported exposure to chromate chemicals.

Studies of workers at a chromate production facility in Painesville, Ohio (*7,8*), and their exposures (*9*) form the primary data used by EPA (*10*) in their quantitative risk assessment of exposure to chromium. These studies used extensive work histories and exposure measurements to estimate risk; EPA used these data in a more quantitative manner. The study cohort consisted of persons employed in the plant for at least 1 year between 1931 and 1936. Exposures were not measured until 1949. An excess risk of lung cancer was detected. Using a proportionate mortality design, it was determined that 18.2% of the plant employee deaths resulted from lung cancer, while only 1.2% of the deaths in the surrounding county resulted from lung cancer. This difference was found to be statistically significant.

Bourne and Yee (*9*) conducted an industrial hygiene investigation to characterize exposures at the Painesville plant in early 1949. Air and settled dust samples were collected throughout the plant. A summary of airborne chromium concentrations (as chromium instead of the more typical CrO_3) in each of the nine production departments is presented in Table 1. Air samples were collected by filtration. All samples were analyzed for hexavalent and trivalent content by polarography: water-soluble species were assumed to be hexavalent, and nonsoluble species were assumed to be trivalent. The magnitude of exposure and the ratio of trivalent to hexavalent species varied widely throughout the plant. The median particle size in the plant was 1.7 μm; the mist in the finish department was 3.4 μm. These particles are well within the respirable range.

To better define worker chromium exposures, Bourne and Yee divided the 128 workers in the plant into 21 groups with similar exposures. One or more personal air samples were collected from each job classification and a time-weighted average exposure calculated. Based on these exposure measurements, jobs were divided into three groups according to the Cr^{3+}/Cr^{6+} ratio of dusts and classified as having predominantly trivalent, mixed

Table 1. Airborne concentrations of hexavalent and trivalent chromium by production department from study of a Painesville, Ohio, chromate facility (*9*).

Production department	Cr concentration, mg/m^3		Ratio Cr^{3+}/Cr^{6+}
	Cr^{3+}	Cr^{6+}	
Ore preparation	1.53	0.04	38:1
Lime and ash	1.20	0.09	13:1
Roast	0.39	0.28	1.4:1
Filtering	0.11	0.09	1.2:1
Neutralizing	0.03	0.06	1:2
Liquor	0.09	0.09	1:1
Finish crystals	0.11	0.28	1:2.5
Chrome cake	0.90	0.22	4.1:1
Shipping	0.31	0.19	1.6:1

trivalent and hexavalent, or predominantly hexavalent exposure. Job histories and exposure information were used to calculate weighted average exposure for workers to the insoluble and soluble fractions and to total chromium. The dose, measured in exposure years (the product of average airborne concentration and duration of exposure at that concentration), was then calculated. Exposures of maintenance workers, who unlike production workers may be exposed anywhere in the plant, were calculated from apportionment of production worker exposures based on the amount of time (measured by maintenance charges) in each work area. Although cases of lung cancer were not observed in the group exposed only to the insoluble species, the small number of persons in the group prevented definitive conclusions. (In this regard, the authors point out that others have stated there is not a risk of disease among miners of the trivalent chromite ore, but reliable data are not available—a situation that still exists today.) Risks to workers were calculated by subdividing according to type and magnitude of exposure.

The first of a continuing series of studies of workers in the British chromate-producing industry was published in 1951 (*11*). This study, conducted in 1949, consisted of a cross-sectional medical screening of 724 active and recently retired workers at three chromate facilities. Radiographic examination revealed one case of lung cancer among these workers. He subsequently died. Another death due to lung cancer was reported to the investigators 13 months later. Although the one incident case per year in this population was greater than the expected 0.44 case, the numbers were judged to be too small to make any definitive statements. It was speculated, however, that the excess risk was probably well below the 25 times increase observed by Mancuso and Hueper (*7*). The investigators state that it was impossible to assess individual exposures in any meaningful way because of frequent job changes by the workers and because of highly variable environmental conditions.

An industrial hygiene survey was conducted of these three British plants (*12*) in conjunction with the medical screening described by Bidstrup (*11*). Single-area grab samples (0.5–5.0 hr duration) were collected at each stage of the production process in each of the three factories. A total of 96 air samples were collected in a dilute aqueous alkali by the impinger method. Samples were analyzed using the standard diphenylcarbazide method. Chromium species soluble in the dilute aqueous alkali were assumed to be hexavalent, and the nonsoluble fraction was assumed to be trivalent. A summary of findings by process area is presented as Table 2. Concentrations are reported to be higher than those reported by Bourne and Yee (*9*), and there are differences in the Cr^{3+}/Cr^{6+} ratios, but differences in the sampling and analytical methods make them difficult to compare. These exposure data were not used in any specific way by Bidstrup (*11*) in the analysis of the epidemiologic data.

As a result of the growing body of information linking exposure in chromate producing industries and lung cancer, the U.S. Public Health Service undertook an extensive environmental, morbidity, and mortality study of seven U.S. chromate plants from 1949 to 1951 (*13*). Epidemiologic study of causes of death is communicated in this report and as a separate publication (*14*). Deaths were investigated through claims paid by insurance companies at these plants over the period 1940 to 1950 (two plants), 1943 to 1950 (one plant), 1946 to 1950 (three plants), and 1949 to 1950 (one plant). Death payments, and thus inclusion in the study, were limited to 1 year after initial claim of disability. It is expected, therefore, that some deaths, including retirees, were missed. A total of 44 death benefits were paid within 1 year of disability claim. Four additional deaths after 1 year were recorded. Raw mortality rates were calculated for each of three age groups. Standardized mortality rates were found to range from 20 to 40, with the highest rate for the youngest workers and the lowest rate for the oldest workers. The epidemiologic data were not evaluated with any additional surrogate measures of exposure.

The U.S. Public Health Service study contained a detailed assessment of worker exposure from data gathered at the seven plants. None of these data were integrated into assessment of mortality and morbidity. Taken as average measures, however, they are indicative of general levels of exposure. Approximately 1600 air samples and 100 settled dust samples were collected as a part of this study. Airborne dust samples were collected in distilled water in standard and midget impingers and generally analyzed by the standard diphenylcarbazide method. Samples were characterized as water soluble, acid soluble/water insoluble, and acid insoluble. Detailed elemental analyses were conducted of the dusts at all stages of the production process. Unlike most exposure assessment of that era, the sample collection strategy was designed to characterize average conditions. Samples were collected over periods ranging from 10 min to almost 3 hr; time-weighted average concentrations for the work day were then calculated.

Table 2. Average concentrations of hexavalent and trivalent chromium by production department from study of British chromate facilities (*12*).

Production department	Cr concentration, mg/m³		Ratio Cr^{3+}/Cr^{6+}
	Cr^{3+}	Cr^{6+}	
Prereaction (mill and mix)	2.14	0.005	430: 1
Roast	0.17	0.029	5.8: 1
Filtering	0.037	0.52	1: 14
Liquor formation	0.014	0.056	1: 4
Drying and shipping	0.0053	0.88	1: 166
Packing	0.0009	0.467	1: 519
Chromic acid	0.036	0.087	1: 2.1
Milling chrome sulfate	0.5	0.003	166: 1
Mixing dichrome and sulfur	—	17.0(?)	—
Milling chrome oxide	0.0006	0.005	1: 8
Chrome tan	—	0.003	—
Waste hopper	0.170	0.002	85: 1

Weighted average exposures for representative job categories are presented in Table 3. Despite the extensive environmental characterization, these data were not factored into the epidemiologic analysis.

A follow-up study of the British cohort was published in 1956 (*15*). The previously studied cohort was followed until 1955 when vital status was determined and a second medical screening conducted on still active workers. Only 4 members of the cohort of 723 were lost to follow-up. A total of 59 deaths were recorded. Twelve deaths were caused by lung cancer; only 3.3 deaths were expected for this population. The resultant standardized mortality ratio (SMR = 363) was statistically elevated. An additional case of lung cancer was detected during the second radiographic screening of current workers. No effort was made to correlate disease experience with any measure of exposure.

Three of the seven U.S. chromate plants were restudied using Social Security Administration records (*16*). The study cohort consisted of 1212 persons employed between January 1, 1937, and December 31, 1940, at these plants. The vital status of the cohort was followed until December 31, 1960. Work histories prior to the start date of the study were unknown. A total of 263 deaths was recorded; 71 deaths were attributed to lung cancer on the death certificates. The resultant SMR (850) was significantly elevated when using the U.S. male population as the reference. Exposure was measured indirectly through duration of employment. Age-specific death rates calculated for groups with various lengths of employment showed a clear dose-response relationship for lung cancer: 73 deaths/100,000 population/year for those employed 0 to 4 years to 6,000 deaths/100,000 population/year for those employed 24 to 29 years, with intermediate terms of employment showing intermediate death rates. While this can be taken as positive evidence of the relationship between exposure to chemicals produced in the chromate process and lung cancer, Taylor (*16*) points out that because of different levels of exposure associated with different jobs and presumed changes in exposure levels over the study period, this relationship cannot be quantified.

Table 3. Average airborne concentrations of hexavalent and trivalent chromium by job title from study of seven U.S. chromate facilities (*13*).

Job title	Cr concentration, mg/m³			Ratio
	Cr^{3+a}	Cr^{6+b}	Cr^{6+c}	Cr^{3+a}/Cr^{6+c}
Ore processors	0.36	0.05	0.01	36:1
Lime and soda ash handlers	0.17	0.03	0.01	17 : 1
Mix room laborers	0.89	0.14	0.04	22 : 1
MIx operators (ore)	0.69	0.06	0.02	35 : 1
Mix operators (residue)	0.08	0.17	0.14	1 : 1.8
Kiln operators	0.05	0.06	0.09	1 : 1.8
Kiln building laborers	0.07	0.07	0.08	1 : 1.1
Crane operators	0.05	0.07	0.14	1 : 2.8
Leach operators	0.04	0.04	0.11	1 : 2.8
Mud operators	0.007	0.01	0.05	1 : 7.1
Residue drier operators	0.03	0.06	0.07	1 : 2.3
Residue mill operators	0.17	0.15	0.07	2.4 : 1
Alumina recovery operators	0.03	0.04	0.06	1 : 2
Evaporator operators	0.007	0.01	0.02	1 : 2.9
Chemical treat operators	0.01	0.05	0.07	1 : 7
Sulfate recovery operators	0.03	0.08	0.12	1 : 4
Liquor concentration operators	0.00	0.02	0.04	—
Centrifuge operators	0.02	0.04	0.14	1 : 7
Drying and bagging operators	0.007	0.02	0.09	1 : 13
Shippers	0.00	0.15	0.02	—
Chromic acid cookers and packers	0.00	0.02	0.03	—
Potash production operators	0.00	0.00	0.17	—
Chromate operators	0.00	0.00	0.04	—
Tanning compound operators	0.00	0.47	0.005	—

[a]Acid insoluble.
[b]Acid soluble/water insoluble.
[c]Water soluble.

The Taylor cohort was subsequently followed for an additional 10 years (*17*). Analysis showed the SMR for lung cancer to remain elevated (942.6) with 69 lung cancer deaths observed versus 7.3 expected. This indicated that risk continued to increase with time. No effort was made to correlate these findings with any measure of exposure, although, based on animal toxicologic information, it was speculated that calcium chromate is the causative agent.

The first study of workers at a Japanese chromate plant was published in 1978 (*18*). This study was based on 487 retired and 67 active workers (at the time the plant closed). The incidence rate for lung cancer in this group was calculated from the time of detection of the first case until 1976. The calculated incidence rate of 657.9 deaths/100,000 population/year was compared to an incidence rate of 13.3 deaths/100,000 population/year for the general Japanese population (SMR = 4900). Exposure information is not provided to help explain this high SMR.

The Baltimore chromate facility, one of the original seven studied (*4,6,13*), was studied in greater detail by Hayes et al. (*19*). This cohort study was designed to resolve questions concerning potential changes in disease incidence resulting from changes in the production process, the risks associated with short-term exposure, and correlation of excess risk with specific production areas. A total of 2101 persons first employed between January 1, 1945, and December 31, 1974, and who were employed for at least 90 days were included in the study. Vital status was followed until July 1977. Age, race, and cause-specific death rates were calculated and compared to local rates. The overall plant SMR for lung cancer was 202. Because of the small number of persons employed in the new plant (after accounting for latency), the data are not clear on the effect of plant changes. The excess risk of lung cancer was not, however, completely eliminated. Although lung cancer was not observed in persons first employed after 1960 (when all of the changes were

completed), the small numbers and the short follow-up make definitive conclusions problematic. Persons with short-term exposure (3 months–2 years) were shown to have elevated risk. A dose-response relationship was demonstrated when duration of exposure was used as a surrogate for exposure. Examination of disease patterns indicated that the risk of disease remained elevated in the wet end of the process and was reduced in the dry end after plant changes. Hayes et al. note that this finding contradicts previous studies, but speculate that the process and exposure controls instituted may have been more effective at controlling exposure in the dry end (*19*). Quantitative exposure data are not presented or incorporated into the analysis of these data.

Satoh et al. (*20*) reported on a different cohort of Japanese chromate workers who had been employed for more than 1 year between 1918 and 1975. Follow-up was until the end of 1978. A total of 120 deaths was recorded. Through analysis of compensation records and death certificates, an elevated risk of lung cancer (SMR = 920) was identified. Incidence was not elevated for any other disease. Analysis of risk by duration of exposure showed a clear dose-response relationship. Quantitative exposure data, however, were not presented to clarify understanding of the excess risk.

Persons employed between 1948 and 1977 at the three British chromate factories were followed until the late 1970s (*21*). A total of 602 deaths (116 from lung cancer) were observed in the study population of 2715 men. A statistically elevated risk of lung cancer was observed. Differences in the production processes between these plants and significant reductions in exposure, assumed to result from the institution of strict process controls in 1954, were exploited to explain observed differences in the lung cancer rate between the plants. Workers were grouped according to exposure: those employed only in the lime-free process instituted at one plant in 1957–59; those employed only in the high-lime process; those employed in both processes or the low-lime process instituted at one of the plants in 1957. Multivariate analysis was used to sort out the effect of process from confounders such as duration of exposure, length of follow-up, year first employed, and age at first employment. Low numbers prevented definitive analysis, but it is stated that this process change had "appreciable effect" in reducing the risk of lung cancer in those engaged in the lime-free process. This is the first epidemiologic study, although not definitive, in which the risk of disease was narrowed to a single chromium compound (calcium chromate).

Abe et al. (*22*) used reported differences in exposures through the chromate production process in an attempt to describe observed differences in cancer cell types. Risk was assessed by comparing months of work time accumulated in each of five work areas to those accumulated by a nasal perforation control group. Twenty cases of lung cancer were examined; 13 were squamous cell, five were small cell, and two were not determined. Squamous cell carcinomas were associated primarily with the roast and leach process (mixed insoluble/trivalent and soluble/hexavalent exposure) and the dichromate manufacturing process (soluble/hexavalent exposure). Small cell carcinomas were associated exclusively with the roast and leach processes. Although actual exposure measurements are not presented or referenced, the authors conclude that the observed cancers are associated with predominant work in areas with exposure to hexavalent chromium compounds (*22*).

Chromium Pigment Manufacture and Use

The wide range of vivid colors produced by various chromium compounds was the stimulus for the start of the chromium industry. Today a significant proportion of the output of chromate manufacturing facilities still goes to the production of pigments. Lead and zinc chromate pigments are the most widely used hexavalent pigments, although many others including strontium chromate, barium chromate, and hydrated chromic oxide (the main trivalent pigment) are used. Most are hexavalent, although their solubility in water varies considerably. Most chromate pigment production begins with sodium chromate or bichromate (formerly in the crystalline form, now usually in solution) to which lead acetate or lead nitrate (depending on the color desired) is added and reacted to form lead chromate. Zinc chromate is formed by reaction of sodium bichromate or chromic acid with zinc oxide. These reactions, which take place in solution, form the pigments as precipitates which must be separated, dried, milled to specified size, and packed for shipment. Chromium pigment exposures are greatest in the latter stages of the process, once the pigment has been dried. Sodium chromate or bichromate exposures are greatest at the beginning of the process. Study of workers in this industry is complicated by simultaneous exposure to chemicals other than chromium. Exposure to chromate pigments may also occur during use, such as spray painting with zinc or lead chromate paints. Assessment of the health effect of these exposures is also complicated by simultaneous exposures to paint solvents, additives, and other pigments.

Despite early case reports of excesses of disease among workers exposed to various chromium-based pigments (*5*), systematic studies of these populations have not been conducted until relatively recently. Langard and Norseth (*23*) studied all 133 workers employed in a Norwegian chromate production company (three plants) between 1948 and 1972. Until 1951 these plants produced lead chromate pigments exclusively. Between 1951 and 1956 they produced lead and zinc chromate pigments, and after 1956, exclusively zinc chromates. Sodium bichromate was the base stock for both these pigments. An examination of the records of all 24 workers with more than 3 years of employment revealed three cases of lung cancer versus 0.079 expected (SMR = 3800). To assess worker exposures, an industrial hygiene study was undertaken concurrently

with the epidemiologic study. Samples were collected for 5 days in each of eight production areas of the three plants. Exposures ranged from 0.01 to 1.35 mg Cr/m^3 and are presented in more detail in Table 4. It is presumed by the authors that the chromium was exclusively in the hexavalent form, although a species analysis was not conducted. Lacking historic exposure information, an attempt was made to characterize previous exposures through interviews with the workers. It is stated that exposures were "the same" throughout the study period. Despite the relatively extensive exposure assessment, an attempt was not made to link the exposure data with the epidemiologic data.

The Dry Color Manufacturers Association commissioned a study of lead chromate production facilities in the U.S. (*24*). Although this study was never published in a peer-reviewed journal, it is frequently quoted. The study involved 577 persons employed at three pigment production facilities for at least 6 months at any time before December 1974. Two of the plants produced lead chromate exclusively and one produced lead and zinc chromate pigments. Fifty-three deaths were reported; 10 persons had died of lung cancer. Analysis by type of pigment exposure (using employment in the different plants as the surrogate) resulted in an SMR = 350 for workers exposed exclusively to lead chromate for more than 10 years prior to 1960 and an SMR = 244 for persons with a mixed exposure over the same time period. Digestive cancers were significantly elevated (SMR = 778) in the plant with mixed exposure, but normal in the other two plants. The authors state that, because of the low number of cases involved, "the findings are consistent with the hypothesis that lead chromate is a respiratory carcinogen, but do not justify any other conclusion" (*24*).

An industrial hygiene survey was conducted simultaneously to estimate worker exposures, although no attempt was made to link these data with the epidemiologic findings (*24*). A total of 62 personal samples was collected over a 1-week period at the three plants. Median 8-hr, time-weighted average concentrations were found to range from 0.02 to 0.06 mg Cr/m^3 at the three plants. Old industrial hygiene records were examined for past exposures, but were of little use because of changes in the sampling and analytical methods employed, the use of area sampling methodologies instead of personal sampling, and changes in the sampling strategy. Review of changes in the process and control equipment permitted the investigators to conclude that the installation of ventilation had reduced exposure at some time in the past, but it was not possible to quantify this reduction or relate it to the health outcomes of the study.

Table 4. Airborne chromium concentrations by work operation measured in three plants producing lead and zinc chromate pigments (*23*).

Work operation	Airborne Cr concentration, mg/m^3		
	Plant A	Plant B	Plant C
Sack filling	0.43	1.35	0.08
Mixing raw materials	0.35	0.33	0.01
Foreman	0.19	0.04	—

Sheffet et al. (*25*) studied 1946 male employees at a New Jersey facility that manufactured lead and zinc chromate pigments. The cohort consisted of all males employed for more than 1 month between January 1, 1940, and December 31, 1969. Because follow-up was incomplete (83%), extensive effort was expended estimating the vital status and disease history of the missing workers. Results presented using several models to account for the missing workers provide mixed conclusions. The incidence of lung cancer was found to be statistically elevated above expected incidence, however, when using most of the models. Stomach and pancreatic cancers, when combined with lung cancer (but not individually) were reported to be in excess. Based on job histories, employee exposures were classified as high (continuous exposure or average > 2.0 mg Cr/m^3), moderate (occasional exposure or average, 0.5–2.0 mg Cr/m^3), or low (infrequent exposure or average < 0.1 mg Cr/m^3). All of the stomach and pancreatic cancers were detected in persons with jobs classified as having high or moderate exposure; 77.4% of the lung cancer cases were so classified. This information must be interpreted very carefully in light of the fact that 72.6% of all workers were classified as having moderate or high exposure. Workers with high exposure for more than 1 year (24% of the cohort) represent 50% of the deaths from stomach cancer, 50% of the deaths from pancreatic cancer, and 45.2% of the deaths from lung cancer.

Another study of lead and zinc chromate production facilities, this time in five European countries, produced mixed results (*26*). This study included persons employed for more than 6 months at these plants between the time recordkeeping became reliable (generally about 1945) and 1976. Because of differences in the plants, their employees, and the recordkeeping systems which prohibited pooling of the population, the investigators were forced to consider each plant separately. Analysis of the causes of death of persons with complete work histories employed for more than 10 years showed elevated SMRs (ranging from 157 to 386) for lung cancer at all five plants. Because of generally low numbers of cases, this excess was statistically significant at only one plant. The data were analyzed using two surrogates for exposure. Analysis by duration of exposure failed to show the expected dose-response relationship. Subjective classification of jobs as having high, moderate, or low exposure showed the greatest risk of lung cancer to be in jobs with high exposure (SMR = 160 for low exposure jobs and SMR = 850 for high exposure jobs). It is not stated on what basis or data jobs were classified. A single case of lung cancer was observed in jobs classified as low exposure. There was a small increase in the risk of lung cancer for jobs with moderate exposure in all plants and the elevated SMR for lung cancer

for jobs with high exposure was statistically significant in all plants.

The population studied by Langard and Norseth (*23*) was reexamined and followed to 1980 (*27*). Lung cancer deaths in the same population of 133 men increased from three to seven. Three of the four new lung cancer deaths occurred among the original subcohort (24 men) employed more than 3 years. The increased risk detected in the subcohort employed more than 3 years (SMR = 3800) and the subcohort employed more than 5 years (SMR = 6000) strengthened previous findings. Again, exposure data or surrogates were not included in the analysis of risk.

Three English plants producing either lead chromate or lead and zinc chromate were studied by Davies (*28*). The study cohort consisted of 1152 men employed for more than 1 year between the 1920s or 1940s (depending on the plant) and 1975. Differences in the production processes and the dates at which exposure controls were introduced were exploited to help understand the exposure-disease relationship. To estimate exposures, workers were divided into groups by date of entry based on the introduction of controls. In addition, jobs were divided by a subjective measure of exposure into high, medium, and low categories (definition changed during study). Standard duration of employment techniques were also used to estimate exposure. Using these subcohorts, excess risk of lung cancer was not detected in the plant producing only lead chromate or in workers with jobs classified as having low exposure in the mixed pigments production facility. For one of the mixed production factories, persons employed in jobs with high or medium exposure for more than 1 year between 1932 and 1954 (when ventilation was installed) were found to be at statistically elevated risk (SMR = 212) of lung cancer as was an equivalent group (i.e., worked before the installation of ventilation controls) in the second mixed production facility (SMR = 444). Persons employed after the installation of ventilation did not exhibit excess risk of lung cancer. Unfortunately, the magnitude of the presumed change in exposure following installation of ventilation is not documented. Short-term workers did not show excess risk of disease in these plants.

The New Jersey population studied by Sheffet (*25*) was reexamined and followed through 1982 (*29*). For this study, the cohort was redefined to include 1879 persons and vital status ascertainment improved to 92%. A total of 453 deaths was observed in this cohort, with no significant excess of cancer at any site. Analysis using duration of employment as a surrogate of exposure, however, indicated a clear dose-response relationship for lung cancer and suggestive (not statistically significant) relationships for digestive and stomach cancers. For lung cancer, the dose-response trends were statistically significant: SMR = 67 for < 1 year employment, SMR = 122 for 1 to 9 years employment, and SMR = 151 for 10+ years employment. For persons who had started work at least 30 years prior to the start of the study, the relationship was even more striking: SMR = 138 for < 1 year employment, SMR = 201 for 1 to 9 years employment, and SMR = 321 for 10+ years employment. Industrial hygiene exposure data collected near the end of the study period showed that persons classified as exposed to have an average exposure of 0.5 mg Cr/m^3 and those highly exposed to have an average exposure of > 2.0 mg Cr/m^3.

Two epidemiologic studies have been conducted of persons using paints with chromate-based pigments. The larger of the two studies involved persons employed as painters in 10 automobile plants (*30*). The cause of 4215 deaths among active or retired workers between 1970 and 1976 was studied. Two hundred twenty-six of these deaths were spray painters; 10 of these were due to lung cancer. Adjusted proportionate mortality analysis failed to show a statistically elevated risk. Further analysis by year of first exposure (in order to satisfy latency requirements) showed similar results. A case-control study of these workers also failed to show a statistically increased relative risk. Exposure data were not included in this study.

A second study of spray painters using paints with zinc chromate pigments was conducted of military aircraft painters (*31*). The study cohort consisted of 977 males who had at least 3 months of employment as a painter at two military bases and who terminated employment between July 31, 1949, and July 31, 1959. Cause of death was determined from death certificates and proportionate mortality compared to U.S. male death rates. Twenty-one of the 202 deaths were caused by lung cancer. The resultant proportionate mortality risk (PMR) of 184 was statistically elevated. Other excesses of disease were noted, but none were statistically significant. To minimize the healthy worker bias inherent in PMR analysis, proportional cancer mortality rates (PCMR) were calculated. The PCMR for lung cancer was reduced to 146, which is not statistically significant. The relationship between disease incidence and exposure was further explored by using duration of employment as a painter as a surrogate for exposure. The analysis showed a "positive gradient" with the longest employed painters having the greatest PMR (300). In addition, analysis of the cohort by time since first exposure showed those first employed more than 20 years previously to have the highest PMR, suggesting a latency period similar to that reported elsewhere. Direct measures of exposure were not employed in the analysis of the disease experience of this cohort. The authors point out that due to the complex nature of exposures associated with paints, it is not possible to definitively identify zinc chromate as the etiologic agent.

Chromic Acid and Chrome Plating

Workers may be exposed to chromic acid as a part of the chromate production process. In addition to the fact that they are typically exposed to many other chromium compounds, these persons usually constitute a

very small proportion of the worker population, making study difficult. Electroplaters using chromic acid in the chrome plating process constitute a much larger group and have a relatively purer exposure (at least to chromium compounds). Chrome plating involves the electrodeposition of metallic chromium on a metal part. The parts to be plated are suspended in a moderately dilute chromic acid bath; the chromic acid serves as the source of chromium. Chromium is present in chromic acid in a highly water-soluble hexavalent form. The primary source of exposure during the plating process is a fine chromic acid mist produced when gaseous bubbles, released by the dissociation of water, rise to the surface of the plating bath and burst.

Waterhouse presented preliminary results of a study of chrome platers who were employed in a British factory after 1946 (*32*). With follow-up of approximately 5000 workers more than 80% complete, a significant excess of lung cancer deaths in males (SMR = 141) had been detected. Other causes of death were not found to be elevated. Information on exposure is not presented except to state that more than half of the workers were classified as "chrome bath workers" with presumed high exposure.

The first systematic investigation of the health experience of chrome platers was made in Great Britain by Royle (*33*). This study included 1363 current and past chrome platers at 54 plants using a case-control design. Sixty-nine deaths had been reported by mid-1972, including 17 from lung cancer and 9 from gastrointestinal cancer. Neither of these causes, although occurring more frequently than in the nonexposed control group, were statistically in excess. The odds ratio for death by all malignant neoplastic diseases, however, was statistically elevated. Except for a notation that more control subjects were exposed to asbestos than noncontrols (potentially increasing the number of lung cancer cases in the controls), exposures of the workers were not quantified in any way in this study. Other studies are cited, however, which attribute exposures ranging from 0.003 to 6.9 mg CrO_3/m^3 to chrome platers.

Metal platers and polishers exposed to chromic acid, among many other chemicals, were studied by Blair (*34*) using a proportionate mortality design. Analysis of the cause of death of 1292 white male members of the Metal Polishers, Buffers, Platers, and Allied Workers International Union who died between 1951 and 1969 revealed a statistically elevated PMR for cancers of the esophagus and liver. The complete lack of specific information on worker exposures and the large number of potential exposures, however, prohibited drawing conclusions regarding exposure and disease. Blair states that this type of study (i.e., with no exposure information) is only useful for hypothesis generation (*34*).

The study of zinc chromate painters described previously (*31*) included a subcohort of 276 male electroplaters employed in two large aircraft repair facilities. As an excess of cancer deaths was not detected in this population, further analysis was not conducted.

Silverstein et al. (*35*) reported on the mortality experience of persons employed for more than 10 years in a die-casting and electroplating plant and who died between 1974 and 1978. A portion of the cohort had chromic acid exposure during plating, although there were many other chemical exposures in the plants. Proportionate mortality assessment of the deaths revealed a statistically significant excess of lung cancer in both male (PMR = 191) and female (PMR = 370) workers. Workers with more than 15 years of employment showed a greater lung cancer PMR than those employed less than 15 years. All other causes of death were in the expected range. In an attempt to isolate the cause of this excess, a case-control approach was used to determine which departments demonstrated an excess of lung cancer. This surrogate measure of exposure revealed that the department encompassing the majority of the die-casting and plating workers had the highest risk of disease. A single air sample collected in 1959 showed chromic acid concentrations to be on the order of 0.5 mg/m^3 in this department, although documentation is not presented to help interpret this exposure. Almost 20 years later, chromic acid concentrations were measured to have been reduced by about 90%. Lacking sufficient comprehensive exposure data, however, the investigators were forced to rely on qualitative statements about what chemicals were known to be present and their relative concentrations. These data were not included in the analysis of the epidemiologic data.

Franchini et al. (*36*) used differences in the magnitude of exposure among different chrome plating plants to explain differences in cause-specific mortality among the plants. The study cohort consisted of 178 persons employed for more than 1 year between 1951 and 1981 in nine Italian chrome plating facilities. Included were 116 persons from "hard" (i.e., thick) plating facilities and 62 persons from "bright" (i.e., thin) plating facilities. The difference in exposure between these two types of facilities was documented with exposure data collected at the plants and as a part of other studies. Chromic acid exposures averaging 0.109 mg^3 near the plating baths and 0.035 mg/m^3 in the middle of the room are cited for hard plating. Concentrations averaging 0.011 mg/m^3 near the plating baths and 0.0047 mg/m^3 in the middle of the room are cited for bright plating exposure. Biological monitoring data (urinary chrome concentration) confirmed this difference and, since biological monitoring pre-dated industrial hygiene monitoring, was used as an index of historic exposures. The overall cancer mortality of the platers was found to be double that expected. Most of these malignancies occurred in the highly exposed hard platers; the incidence of lung cancer was statistically elevated in this group and that of stomach cancers approached significance.

Twelve years after preliminary reports of the Waterhouse study had been presented (*32*), the completed study was published (*37*). The original cohort was altered in this study to include 2689 persons employed as nickel/chromium platers at a large British automobile

bumper manufacturing facility between 1946 and 1983. Analysis of cause-specific mortality showed cancer of the stomach (SMR = 154), liver (SMR = 500), nose and larynx (SMR = 1000), and lung (SMR = 150) to be statistically elevated above expected. The relationship of these diseases to duration of employment, the only measure of exposure available, when examined through the use of regression models and life table analysis, showed a positive relationship for lung cancer only. An additional group surrogate measure of exposure, the known high rate of nasal perforations in one part of the factory, was investigated, but a relationship with excess mortality was not demonstrated.

Ferrochromium Production/Welding

Ferrochromium (mostly stainless steel) is produced by the electrothermal reduction of chromite ore with coke in the presence of iron in electric arc furnaces. This process produces copious amounts of smoke and other particulates. Some of the trivalent chromite ore is oxidized to the hexavalent form during the process; most of the ore, however, is reduced to chrome metal. Ferrochromium workers are exposed to a number of metallic fumes, products of combustion, and (historically) asbestos used to insulate the arc furnaces. Persons welding stainless steel or using stainless-steel welding rods (the most common welding rod used), may also be exposed to chromium. There are at least 10 major types of welding. Worker exposures to metal fumes, fluxes, and gases produced may vary greatly depending on which type of welding is done. Large differences in chromium concentrations, and the proportion of the chromium converted to the hexavalent form, have been demonstrated using different types of welding. In addition, exposures vary depending on what type of metal is being welded.

The first investigation of the causes of death of persons employed in ferrochromium production used a cohort of 946 men employed in a Norwegian ferrochromium and ferrosilicon facility (*38*). Only persons employed for more than 6 months between 1946 and 1970 were included in the study. Vital status of the cohort was determined as of 1977. Worker exposures were classified according to the job title held for the longest time. An industrial hygiene assessment of exposures in 1975 (using personal samples analyzed by the diphenylcarbazide method) demonstrated mean chromium exposures in the ferrochromium department to be between 0.01 and 0.29 mg Cr/m^3. Hexavalent species are reported to constitute 11 to 33% of this total, although the proportion is not specified by work operation. Although chromium exposure is not reported for the ferrosilicon department, it is unclear whether it was actually measured. Historic exposures are not estimated, although the occurrence of nasal perforations in the past is said to indicate hexavalent chromium concentrations in excess of 0.1 mg/m^3. Sixty-four cancers, including nine lung cancers, occurred up to 1977. The resultant lung cancer rate was not statistically elevated when compared with national or local county death rates. When compared to the ferrosilicon workers, however, the rate was statistically in excess of expected (SMR = 850). The exposure data were not used in the epidemiologic analysis other than to confirm exposure status.

A parallel Swedish study (*39*) reached different conclusions than the Norwegian study. This study of 1876 ferrochromium workers examined deaths occurring between 1951 and 1975 in a group of men employed for more than 1 year after 1930. Incidence rates resulting from 166 cancer deaths, including 9 lung cancers, were calculated and compared to local rates. The incidence rates for all malignancies and for lung cancer, including lung cancers in the highly exposed arc furnace worker subcohort, were within the expected range. Maintenance workers with less than 15 years of employment demonstrated a statistically elevated incidence of lung cancer. Two of the four cases classified as lung cancer in this group, however, were actually mesotheliomas. In fact, three of the cancer deaths in the cohort were due to mesothelioma. Plant records document that asbestos was used at a rate of 2100 kg/year during the time these cases were employed. Although jobs were divided into four exposure classes through a survey (not presented) and worker interviews, the authors frankly admit the classifications to be only approximations. Consequently, they were not used in data analysis.

In the only community-based study of the relationship between chromium exposure and disease, Axelsson and Rylander (*40*) examined the incidence of lung cancer among residents of a Swedish county containing two ferrochromium production plants. An increase in the incidence of lung cancer was found to be associated with increasing population density. When this factor was controlled for, however, the incidence of lung cancer in the two towns with the ferrochromium facilities was indistinguishable from the rest of the county. Exposure of the county residents was estimated from measurements made as a part of the Swedish air pollution monitoring network during the 4 years preceding the study. Total chromium concentrations at the five monitoring stations nearest the facilities ranged from 100 to 400 ng/m^3 as a monthly average. Rural concentrations were reported to be 50 to 100 times lower.

Follow-up was extended on the population of Norwegian ferrochromium and ferrosilicon workers an additional 7 years to the end of 1985 (*41*). The cohort was expanded to include 1235 persons employed before 1965. Deaths occurring from January 1, 1953, to December 31, 1985, were analyzed. The same cohort methodology was employed. Job classifications remained unchanged. Additional exposure data were not presented, and the existing data were not incorporated in the analyses. Cancer of the lung, prostate, and kidney were in excess in the ferrochromium workers; this excess, however, was still in the range of statistically expected cases when using national and local rates. The excess for lung cancer, as in the previous study, is significantly larger (SMR

= 256) when compared to the ferrosilicon workers. Lung cancer rates are reduced from the previous study, perhaps the authors speculated, from a reduction in exposure.

The risk of disease for persons exposed to chromium through the welding of stainless steel was examined in a study of eight Swedish companies (*42*). The study cohort consisted of 234 persons who welded stainless steel for more than 5 years between 1950 and 1965. Persons who welded in shops where asbestos was used extensively were excluded from the cohort. The majority of these workers used covered electrodes. The number of expected and observed deaths, both from all causes and from all malignant neoplasms, was equal. The risk of lung cancer, however, was significantly elevated (SMR = 440). This risk was based on three cases, all of different cell types, all in smokers or former smokers. Two cases used covered electrodes and one used shielded electrodes. A comprehensive survey of welding exposure in Sweden is referenced in this article, although it is unclear whether the plants studied were also the subject of the epidemiologic study. The exposure data, which were collected in 1975, clearly document higher chromium exposures resulting from covered arc welding as compared to gas shielded welding (median exposures of 0.210 mg Cr/m^3 for covered electrodes and 0.020 mg Cr/m^3 for shielded electrodes). In addition, it is stated that a greater proportion of the welding fume from covered arc welding is soluble hexavalent chromium than from shielded arc welding. Historic exposures (1950 to 1965) of the cohort were evaluated through worker interviews to be the same or higher.

Becker et al. (*43*) conducted a study of stainless-steel welders using nickel/chromium electrodes who were first exposed from 1950 to 1970 in 25 German factories. This case control study included 1221 welders and 1694 controls. Seventy-seven deaths (six from lung cancer) were observed in the welder population. While the SMR for lung cancer was within the range of expected values in this population, the rate for deaths due to all malignancies was found to be statistically elevated. It is also noted that there were two deaths from mesothelioma, usually regarded as a marker of asbestos exposure (another cause of lung cancer) in this population. The only linkage of exposure estimates to health outcomes in this study was through the comparison of disease in welders doing covered arc welding and gas shielded welding. Although the SMR was lower than expected for most causes of death (and never significantly elevated) for covered arc welding, it was always greater than that for shielded gas welding.

There is only one epidemiologic study of exposure to chromium metal (*44*). This study cohort consisted of 1164 males employed for more than 3 months between 1927 and 1981 in a facility manufacturing stainless-steel sinks and saucepans. Deaths between 1951 and 1983 were analyzed. One hundred ninety-four deaths occurred in the population; 63 deaths occurred in a subcohort of 318 persons employed for more than 5 years and for whom follow-up was more than 20 years. The observed death rates were within expected ranges except for an excess (SMR = 247) of deaths from colon and rectal cancer in the subcohort. Exposure measurements were made in the late 1970s. Metallic chromium concentrations were found to average 0.1 mg/m^3 for grinding and 0.01 mg/m^3 for polishing. Exposures were said to be higher prior to the 1950s. Although chromium exposure data are presented, the authors state that, because of numerous other exposures including the grinding and polishing compounds as well as nickel, it is not possible to implicate any one substance as being related to disease.

Conclusions

Because of the lack of adequate worker exposure data, epidemiologic studies of diseases produced as a result of exposure to various chromium compounds are not able to distinguish the risks attributable to the individual compounds, nor are they able to quantify the exposure-risk relationship in more than the crudest manner. Despite long-term recognition of these diseases, exposure data have not been generated to help resolve lingering questions of what chromium compounds in what amounts cause what diseases.

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